Papers and Originals

Mortality from Cancer and Other Causes after Radiotherapy for Ankylosing Spondylitis

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In 1955 the Medical Research Council requested us to investigate the incidence of leukaemia in man following exposure to ionizing radiations, and to examine the nature of the relationship between the dose of radiations and the extent of the incidence of the disease. With the help of a large number of radiotherapists and other colleagues[1] we chose for investigation patients who had been given radiotherapy for ankylosing spondylitis during the period 1935–54, and extracted details relating to them from the records of 81 radiotherapy centres. Estimates of the numbers of patients receiving different doses were obtained from the records of a stratified sample of approximately one in six of all the patients, and the subsequent incidence of leukaemia was determined: (1) from existing follow-up records, (2) by an appeal for information in the medical journals, and (3) by matching the names of the treated patients with a nominal roll of all patients known to have died of leukaemia or aplastic anaemia in the British Isles between 1945 and 1955 (Medical Research Council, 1956 ; Court Brown and Doll, 1957).

The method used to discover the incidence of leukaemia was chosen because it enabled a result to be obtained quickly. It proved to be highly efficient (see footnote 6), but the lack of a complete follow-up meant that no estimate could be made of mortality rates from other diseases. In particular, no reliable information was obtained about the incidence of other forms of cancer. Other cancers could not be studied in the same way, because so many deaths were involved, and information about the mortality attributed tc these cancers has had to wait until all the patients have been followed individually.

We now report the results obtained by following the patients until 1 January 1960—that is, over a follow-up period which varies for individual patients from 5 to 25 years. During the follow-up we have had the opportunity of re-examining the radiotherapy records and have added a few patients whose notes had previously been overlooked. We have also been able to make the series more complete by adding material from a few other radiotherapy centres which, for one reason or another, had not been able to co-operate previously ; and we have made it more accurate by demonstrating at follow-up the identity of a few patients whose repeated attendances had been attributed to two or more individuals.

Data

Patients were included in the study if they had been treated for ankylosing spondylitis (International List No. 722.1) during the years 1935–54 at any one of 87 radiotherapy centres in Great Britain and Northern Ireland. All 76 centres at which radiotherapy was provided by the National Health Services on 28 July 1955 were included, as were 10 which had previously given radiotherapy, but which had ceased to do so, and one which provided radiotherapy privately outside the Service. The co-operation of this last centre was particularly helpful, as it was the first to use radiotherapy for ankylosing spondylitis, and many spondylitic patients who attended at it in the 1930s had been treated with wide-field irradiation to the whole trunk.

Patients were excluded from the series only if it would have been difficult or impossible to obtain the relevant details of their *x*-ray dosage or subsequent history—that is, if: (1) they had previously been given radiotherapy abroad, in private, or before 1935 ; (2) they were known to be living abroad at the time of their first treatment ; or (3) their radiotherapy notes were missing or grossly incomplete.

There remained 14,554 patients for study.[2] Table I shows the numbers separately for each sex who first came under observation in each year. Table II shows the numbers known to have died or emigrated before 1 January 1960 and the proportion lost to follow-up. It also shows that adequate follow-up information was obtained in more than 98% of all cases.

TABLE I.—*Number of Patients Studied by Sex and Year of First Observation*

Year of First Observation	No. of		Total No.
	Men	Women	
1935	27	8	35
1936	30	7	37
1937	53	14	67
1938	82	27	109
1939	116	34	150
1940	112	31	143
1941	136	33	169
1942	253	33	286
1943	436	58	494
1944	630	67	697
1945	698	94	792
1946	804	136	940
1947	790	174	964
1948	987	212	1,199
1949	1,232	233	1,465
1950	1,250	267	1,517
1951	1,171	299	1,470
1952	1,175	241	1,416
1953	1,146	200	1,346
1954	1,033	225	1,258
All years ..	12,161	2,393	14,554

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[1] See Court Brown and Doll (1957), Appendices E and F.

[2] The precise number of patients excluded is not known as some of their records were destroyed after our initial report (Court Brown and Doll, 1957). It is, however, certainly less than the 432 that we originally reported, as patients treated previously at one large clinic outside the National Health Service have been brought into the study, and the number excluded because of missing or incomplete radiotherapy records has been reduced to 83.

The cause of death certified on the death certificate was obtained for all but two of those who died, and the deaths were classified according to the detailed International List (World Health Organization, 1957).

TABLE II.—*State of Patients at End of Follow-up Period* (1 *January* 1960)

State at 1 January 1960	Patients	
	No.	Percentage of Total
Alive	12,358	84·9
Emigrated	362	2·5
Died	1,582	10·9
Not known	252	1·7
All states	14,554	100·0

Observations

Expected Mortality

The numbers of deaths that would have occurred if the patients had suffered only normal mortality rates were estimated by multiplying the person-years at risk by the corresponding national mortality rates for England and Wales.

The numbers of person-years at risk were first calculated separately for each sex, each five-year age group, the six-year period 1935–40, and each quinquennium from 1941–5 to 1956–60. Patients were counted as being at risk for half a year in the year in which they first came under observation, and those who died or emigrated were counted as being at risk for half a year in the year in which they ceased to be under observation. Those few patients whose status was not known on 1 January 1960 were assumed to have been still alive. The numbers at risk in each subgroup were then multiplied by the sex and age-specific mortality rates for the corresponding period.[3] For this purpose use was made of rates which had previously been calculated (McKenzie, Case, and Pearson, 1957; Case and Pearson, personal communication) and which covered all causes of death combined, all cancers, the principal separate types of cancer, and the principal respiratory diseases. Mortality rates for other diseases were calculated from data published in the Registrar-General's annual reports. For several of the individual causes of death, however, separate data had been published only since 1949—that is, for ankylosing spondylitis, amyloid disease, ulcerative colitis, non-rheumatic chronic endocarditis, and aplastic anaemia—and for these causes it was assumed that the rates prior to 1951 were equal to those in 1949–50,[4] with a small adjustment to make the sum of all the mortality rates equal to the known mortality from all causes. The error resulting from the lack of complete information for the years before 1949 is, however, negligible, since only 11% of the total deaths occurred during this period.

Comparison of Observed and Expected Mortality

Table III shows that the total death rate among the patients was approximately 1.8 times as high as the corresponding national death rate in England and Wales. The excess mortality was, however, not distributed evenly among all disease groups, but varied from one-tenth of the national rate (cancer of lightly irradiated sites) to nearly 1,000 times the rate (ankylosing spondylitis). Several factors are likely to have contributed to the high mortality, and the disease groups shown in Table III have been divided into four principal classes corresponding to the different types of factor.

Class A includes deaths directly attributed to arthritis and other forms of rheumatism, excluding rheumatic fever. As would be anticipated, the mortality from these causes is greatly increased compared with the national experience. The majority of the deaths were attributed directly to ankylosing spondylitis (89), but a substantial number were attributed to other or less exactly specified rheumatic conditions (52)—that is, rheumatoid arthritis (18), spondylitis not specifically described as ankylosing (6), spinal arthritis (3), osteoarthritis (17), and arthritis (8). The occurrence of excess deaths due to these latter causes can be attributed partly to the inclusion of patients with forms of rheumatism other than ankylosing spondylitis in the group of patients originally studied and partly to inaccurate or incomplete certification of the cause of death.

TABLE III.—*Number of Deaths Observed and Expected, by Cause*

Disease Class	Cause of Death	No. of Deaths		Observed Deaths Divided by Expected
		Observed	Expected	
A	Ankylosing spondylitis ..	89	0·09	988·9
	Other arthritis and rheumatism	52	1·23	42·3
	Total	141	1·32	106·8
B	Amyloid disease	6	0·20	30·0
	Ulcerative colitis	25	1·32	18·9
	Nephritis	47	13·89	3·4
	Pulmonary tuberculosis ..	131	44.66	2.9
	Chronic endocarditis, not specified as rheumatic ..	17	6·02	2·8
	Pneumonia	70	27·39	2·6
	Other respiratory disease ..	39	15·35	2·5
	Cancer of colon	25	14·78	1·7
	Total	360	123·60	2·9
C	Aplastic anaemia	15	0·51	29·4
	Leukaemia	52	5·48	9·5
	Cancer of heavily irradiated sites	200	127·27	1·6
	Total	267	133·25	2·0
D	Other gastro-intestinal disease	39	16·97	2·3
	Peptic ulcer	25	15·06	1·7
	Other disease	105	67·10	1·6
	Cerebrovascular disease ..	94	74·98	1·3
	Bronchitis	71	56·36	1·3
	Violence	86	67·58	1·3
	Other circulatory disease ..	332	257·35	1·3
	Cancer of lightly irradiated sites	60	52·42	1·1
	Total	812	607·83	1·3
	Cause unknown	2	—	—
All classes	All causes	1,582	866·00	1·8

Class B includes deaths attributed to conditions that are known to be clinically associated with ankylosing spondylitis. Non-rheumatic chronic endocarditis and perhaps ulcerative colitis may be attributed directly to the same process that gives rise to spondylitis. Amyloid disease is a secondary complication, and the excess of deaths attributed to nephritis may in fact be due to unrecognized amyloid disease of the kidneys (Cruickshank, personal communication[5]). Pulmonary tuberculosis, pneumonia, and other respiratory diseases, excluding bronchitis, have long been recognized as being associated with ankylosing spondylitis, and their high fatality is presumably related to immobility of the chest. Deaths attributed to these conditions may, however, also include a small number due to a type of upper-lobe fibrosis that is part of the primary pathological process (Campbell and MacDonald, 1965). Cancer of the colon is included in this group because it is an important complication of ulcerative colitis. Much of the colon must, however, have been irradiated from radiotherapy given to the lumbar spine and sacro-iliac joints, so that radiation may also have been a contributory cause. In practice the contribution of ulcerative colitis to the risk of cancer of the colon is unlikely to have been great. If ulcerative colitis occurs normally in 2 per 1,000 of the population and the incidence is increased twenty-fold in spondylitis (as is suggested by the increase in mortality),

[3] Rates for the quinquennium 1936–40 were assumed to have held for the period 1935–40.

[4] For amyloidosis and ankylosing spondylitis the rates for 1958–9 had to be used throughout.

[5] Professor B. Cruickshank has reviewed the pathological findings in all patients in the series who came to necropsy, and will be reporting his results separately.

and the risk of colon cancer is increased tenfold in subjects with ulcerative colitis, it follows that the risk of colon cancer in spondylitis must be expected to be about 36% greater than normal, and any excess above this might be attributable to other causes.

Class C includes conditions which may be due to the treatment with ionizing radiations, rather than to the original disease. An increased mortality from leukaemia and aplastic anaemia among these patients has been reported previously (Court Brown and Doll, 1957), and further experience has provided very similar results. Both conditions have a high fatality rate, and individual follow-up of all patients has revealed very few cases not already known from mortality records.[6] One patient was found to be alive with leukaemia when the follow-up was completed (1 January 1960), four patients were found to have had leukaemia, and eight to have had "aplastic anaemia," whose deaths were primarily attributed to some other cause. Several of the patients recorded as having had "aplastic anaemia" were, however, found to have had undiagnosed aleukaemic leukaemia (Court Brown and Doll, 1957), and the amount of true aplastic anaemia associated with irradiation must be substantially less than the figures imply. Conversely, the amount of leukaemia must be somewhat more.

Cancer other than leukaemia has not previously been reported as a complication of radiotherapy for ankylosing spondylitis. In the present study the principal types of cancer were divided —without knowledge of the results—into two groups according to whether the organ of origin was or was not likely to have received a substantial amount of radiation from a standard course of radiotherapy to the whole spine and sacro-iliac joints. The brain and central nervous system, mouth, liver and gall-bladder, rectum, breast, uterus, prostate, testes, kidneys, and urinary bladder are classified as lightly irradiated sites and all others as heavily irradiated. The division is not always clear-cut and leads to some anomalies which could not be avoided. The spinal cord, for example, must have been heavily irradiated. Deaths from tumours of this site are, however, relatively rare, and it is difficult to obtain an estimate of the number expected separately from the number attributed to tumours of the brain, so that the whole group, "brain and other parts of the central nervous system," was classed as being lightly irradiated. Conversely, much of the skin and skeletal system was outside the range of the direct beam of irradiation, and these sites could have been classified as lightly irradiated rather than heavily. In a few centres, moreover, patients had been treated with whole-body irradiation or with "pelvic baths," and in these patients the rectum, uterus, prostate, and urinary bladder will have received doses comparable to those received by other "heavily irradiated" organs. The number of patients treated by these methods is, however, relatively small, so that for the group as a whole these sites can be regarded as having been lightly irradiated.

The relative increase in mortality from cancers in heavily irradiated sites is not large compared with that observed for some other conditions; but the normal mortality from these cancers is high and the excess number of deaths attributed to them (73) is slightly greater than the excess number attributed to leukaemia and aplastic anaemia combined (61).

Class D includes conditions for which the mortality might have been expected to be normal or close to normal. In fact all the conditions studied showed some increase in mortality, and, though the increase was not in general large, the total experience was sufficiently great for the increase of deaths in this group to be statistically highly significant.

Mortality at Different Periods after Irradiation

Further evidence about the reasons for the increased mortality can be obtained by examining the relationship between the date of treatment and the date of appearance of the excess deaths. This is indicated in Table IV. Data are given separately for cancer, aplastic anaemia, and all other causes of deaths combined, and the observed numbers of deaths are shown for three-year periods up to a final period 15 to 24 years after entry (see footnote to Table IV). For the great majority of patients the date on which they came under observation in the series corresponds to the date of first treatment. For a few patients, however, there was evidence that radiotherapy had been given previously at some other centre, but the earlier treatment had not brought the patient under observation (either because the initial records had not been found or because treatment took place at a centre not included in the survey). The proportion of patients who had received radiotherapy before the date of entry (2.4%) is, however, small, and for the present purpose can be ignored.

The results show that the pattern of the time-relationship varies for different groups of diseases. For all causes of death other than cancer and aplastic anaemia the mortality rate bears a practically constant relationship to the expected mortality, varying only from 1.7 to 1 in the first two and a half years to 2.1 to 1 after 12 to 14 years (Table V). In contrast, the relationships for leukaemia, aplastic anaemia, and cancer of heavily irradiated sites show evidence of a trend with time. For leukaemia and aplastic anaemia the mortality increases between the first and second periods and then falls off, the

[6] Only one patient was discovered who developed leukaemia before the end of 1955 and who was overlooked in our previous report. He died of leukaemia in 1948, but this was not recognized owing to a transcription error which led to the belief that he was still alive some time later.

TABLE IV.—*Numbers of Deaths Observed and Expected, by Cause and Period After First Observation*

Cause of Death	No. of Deaths	Years after First Observation*						All Periods
		0–2	3–5	6–8	9–11	12–14	15–24	
Leukaemia	Observed	7	19	14	6	5	1	52
	Expected	1·10	1·49	1·32	0·86	0·45	0·27	5·48
Aplastic anaemia	Observed	3	7	4	1	0	0	15
	Expected	0·11	0·14	0·12	0·07	0·04	0·02	0·51
Cancer of heavily irradiated sites	Observed	33	36	46	46	27	12	200
	Expected	22·48	33·25	31·32	21·16	11·54	7·52	127·27
Cancer of colon	Observed	6	8	4	5	1	1	25
	Expected	2·94	3·96	3·52	2·33	1·21	0·82	14·78
Cancer of lightly irradiated sites	Observed	13	15	13	12	2	5	60
	Expected	10·27	14·09	12·64	8·27	4·28	2·88	52·42
All other causes	Observed	234	336	290	191	113	66	1,230
	Expected	139·07	178·56	155·45	102·30	54·22	35·93	665·56
All causes ..	Observed	296	421	371	261	148	85	1,582
	Expected	175·97	230·49	204·37	135·99	71·74	47·44	866·00
No. of person-years at risk ..		35,453	40,746	31,906	19,247	9,558	4,886	141,796

* The year after first observation was calculated by subtracting the calendar year in which the patient first came under observation from the calendar year in which he was subsequently observed. Since patients first came under observation, on average, half-way through the calendar year, the first "three-year period" covers, on average, only two and a half years—and varies for different individuals from two to three years. The next four periods each cover three years for all individuals, but the actual periods observed vary slightly—for example, for a man who entered on 1 January of any year the second period covers the fourth, fifth, and sixth years and for a man who entered on 31 December it covers the third, fourth, and fifth years.

reduction being more marked for aplastic anaemia than for leukaemia. For cancer of heavily irradiated sites the mortality is at first higher than expected, falls to near normal levels at three to five years after entry, and then rises to more than twice normal 9 to 14 years after entry.

TABLE V.—*Number of Observed Deaths Expressed as a Proportion of the Number Expected, by Cause and Period After First Observation*

Cause of Death	Years after First Observation						All Periods
	0–2	3–5	6–8	9–11	12–14	15–24	
Leukaemia	6·4	12·8	10·6	7·0	11·1	3·7	9·5
Aplastic anaemia	27·3	50·0	33·3	14·3	0·0	0·0	29·4
Cancer of heavily irradiated sites	1·5	1·1	1·5	2·2	2·3	1·6	1·6
Cancer of colon	2·0	2·0	1·1	2·1	0·8	1·2	1·7
Cancer of lightly irradiated sites	1·3	1·1	1·0	1·5	0·5	1·7	1·1
All other causes	1·7	1·9	1·9	1·9	2·1	1·8	1·8
All causes ..	1·7	1·8	1·8	1·9	2·1	1·8	1·8

The increased mortality from cancer of heavily irradiated sites in the first few years after entry is in all probability an artifact due to misdiagnosis. Several of the patients who died within a year or so from carcinoma of the stomach, pancreas, lung, or prostate had presented with pain in the back, and there is reason to believe that in these patients back pain was produced by tumour involvement of the spine, either by direct spread or by secondary deposits, and was mistaken for that caused by spondylitis. In retrospect it is clear that the presenting symptoms had been due to cancer and not to spondylitis.

The number of deaths more than 15 years after entry is small, and the fall in mortality compared with the previous period is not statistically significant. Further evidence about the nature of the relationship at this period can, however, be obtained by a preliminary examination of the results of prolonging the follow-up period for a further three years to 1 January 1963. Certain knowledge of the status of the patients at this date has been obtained for only 41%, but the annual numbers of deaths recorded in the last three years are not very different from those recorded in the three previous years (1957, 187 ; 1958, 170 ; 1959, 178 ; 1960, 151 ; 1961, 148 ; and 1962, 115), and it seems probable that we already know about three-quarters of the deaths that occurred. If, therefore, we assume that all those not known to have died or emigrated were still alive and in the British Isles on 1 January 1963, and recalculate the expected mortality on this basis, our results will be biased by somewhat underestimating the mortality rate among the patients and somewhat (but very slightly) overestimating the expected mortality. The results may, however, give us more useful information about mortality rates more than 15 years after entry, because the relevant numbers of person-years under observation will have been doubled (nearly 10,000 against less than 5,000).

The results given in Table VI now show that the ratio of the observed and expected mortality is practically the same at all periods more than eight years after entry to the study (2.1 to 1, 2.3 to 1, and 2.2 to 1), and that the absolute excess mortality from cancer of heavily irradiated sites continues to increase (1.27 per 1,000 persons per year at 9 to 11 years after entry ; 1.69 per 1,000 at 12 to 14 years after entry ; and 1.98 per 1,000 at 15 or more years after entry). It may be noted also that, in contrast to the results for cancers of heavily irradiated sites, the provisional results of the extended follow-up confirm the suggestion that the excess mortality from leukaemia and aplastic anaemia had passed its peak within 15 years of coming under observation.

Cancers of lightly irradiated sites show no significant increase in overall mortality, and, as would be expected, provide no evidence of any unusual trend in incidence with the passage of time. Cancer of the colon also shows no definite evidence of a trend, but the number of excess deaths due to this condition is small.

Cancers at Individual Sites

Though there were 200 deaths attributed to cancers of heavily irradiated sites (269 when the follow-up is prolonged to 1 January 1963), the numbers attributed to most of the individual types of cancer are small. It is, however, of some interest to see whether the excess mortality can be wholly explained by an increase in a few specific cancers or whether it is spread widely over a large number. We have already suggested that the increased mortality in the first two and a half years is likely to be an artifact, and we have shown that the

TABLE VII.—*Numbers of Deaths Observed and Expected from Cancer of Heavily Irradiated Sites Six or More Years After First Observation, by Site*

Primary Site (Death Certification)	Completed Follow-up at 1 January 1960			Incomplete Follow-up at 1 January 1963		
	No. of Deaths		Observed as Proportion of Expected	No. of Deaths		Observed as Proportion of Expected
	Observed	Expected		Observed	Expected	
Pharynx	4	0·70	5·7	5	1·05	4·8‡
Oesophagus ..	3	2·25	1·3	3	3·37	0·9
Stomach	28	16·03	1·7	38	23·62	1·6‡
Pancreas	9	3·78	2·4	12	5·71	2·1‡
Larynx	1	1·23	0·8	2	1·81	1·1
Bronchi	59	35·65	1·7	96	54·20	1·8‡
Ovaries	1	1·44	0·7	4	2·16	1·9
Skin	0	0·95	0·0	0	1·37	0·0
Bones	2	0·79	2·5	5*	1·11	4·5‡
Hodgkin's disease	1	1·78	0·6	1	2·47	0·4
Other lymphatic and haemopoietic tissues	7	2·30	3·0	10†	3·39	2·9‡
Others	16	4·62	3·5	24	6·78	3·5‡
Heavily irradiated sites	131	71·53	1·8	200	107·04	1·9‡

* The reliability of the diagnosis of primary bone tumour on a death certificate is not high. Only three deaths have been confirmed as due to bone sarcoma ; the expected number of deaths is estimated from data given by Mckenzie, Court Brown, Doll, and Sissons (1961) to be 0·63.

† Seven cases of lymphosarcoma or reticulosarcoma, one of lymphoma unspecified, and two of myelomatosis. Leukaemia is not included in this category (see Tables V and VI).

‡ Difference between observed and expected statistically significant—$P < 0·025$ on a one-tailed test.

TABLE VI.—*Comparison Between Numbers of Deaths Observed and Expected, by Selected Causes and Period After First Observation : Incomplete Follow-up to 1 January 1963*

Cause of Death	Years after First Observation						All Periods
	0–2	3–5	6–8	9–11	12–14	15–27	
Leukaemia*:							
Observed deaths	7	19	16	10	7	1	60
Expected „	1·10	1·49	1·59	1·27	0·76	0·54	6·75
Observed as proportion of expected	6·4	12·8	10·1	7·9	9·2	1·9	8·9
Aplastic anaemia*:							
Observed deaths	3	7	5	1	0	0	16
Expected „	0·11	0·14	0·14	0·11	0·06	0·05	0·61
Observed as proportion of expected	27·3	50·0	35·7	9·1	0·0	0·0	26·2
Cancer of heavily irradiated sites:							
Observed deaths	33	36	52	67	46	35	269
Expected „	22·48	33·25	38·55	32·52	20·29	15·67	162·76
Observed as proportion of expected	1·5	1·1	1·3	2·1	2·3	2·2	1·7
No. of man-years at risk ..	35,453	40,746	37,363	27,082	15,221	9,766	165,631

* Although all patients have not been followed individually until 1 January 1963, the total number of deaths is probably known, as the names of the untraced patients have been checked against a nominal role of persons dying of these conditions.

observed mortality is very close to the expected mortality three to five years after entry. Clearly, therefore, we are interested only in the results obtained after six or more years. These are shown in Table VII, both for the period up to 1 January 1960, when follow-up is almost complete, and for the longer period to 1 January 1963, when the results were biased by underestimating the actual deaths and overestimating the number expected. From Table VII it is evident that the greatest absolute excess occurred with cancer of the lung, followed at a considerable distance by a miscellaneous group (mainly carcinomatosis, primary unknown), cancer of the stomach, tumours of the lymphatic and haemopoietic system other than Hodgkin's disease or leukaemia, and cancer of the pancreas. For all these and for cancers of the pharynx and of the bones the observed excess is statistically significant ($P<0.025$ on a one-tailed test). There is, however, very little difference in the ratio of the numbers of deaths observed and expected, which varies only from between 4 and 5 to 1 (cancer of the pharynx and bones) to less than 1 to 1 (cancer of the oesophagus, Hodgkin's disease, and cancer of the skin).

Interpretation

Mortality Associated with Disease Process

The increased mortality from conditions in classes A and B (Table III) can presumably be attributed to the effects of the disease for which the patients were treated. It is possible that some of the increase may be due to the effects of treatment—some cases of cancer of the colon, for example, may have been due to local irradiation—but in the absence of any compelling reason to the contrary we may assume that the abnormal mortality is due to the disease.

The proportionately small but statistically highly significant increase in deaths due to conditions in class D (conditions not grossly related to spondylitis or to irradiation) is more difficult to explain. Several reasons can, however, be suggested.

First, the broad disease groups may contain a small proportion of rare conditions which are in fact directly due to the disease. The large group of "other circulatory diseases," for example, contains 43 deaths attributed to "chronic rheumatic heart disease," including seven specifically described as due to lesions confined to the aortic valves. The total number of deaths expected in this category was approximately 22, only one or two of which would normally be attributed to aortic lesions alone, so that some of the excess cardiac mortality—and perhaps a substantial part—may be due to the aortic lesion characteristically associated with spondylitis. Similarly, the deaths due to "other gastro-intestinal disease" include two due to regional enteritis, which bears some relationship to ulcerative colitis and is also associated with spondylitis, and three attributed to non-specific gastro-enteritis or colitis. Violence may also contain some deaths secondarily related to the disease. Spondylitic patients may be more prone to accidents in general, but they are certainly susceptible to a characteristic injury in which the atlas is dislocated and death is caused by pressure of the odontoid process on the medulla (Kellgren, personal communication). Several cases of myelitis and bulbar palsy may have been due to this type of injury, as may some of the deaths attributed to injury in motor crashes.

Secondly, the presence of complications such as amyloid disease and nephritis may lower vitality and increase the risk of death from other unrelated causes.

Thirdly, the cause of death given on the death certificate is not always accurate, and the increased mortality from conditions in classes A, B, and C must be expected to spill over into class D, causing a spurious appearance of increased mortality from genuinely unrelated diseases.

Fourthly, ionizing radiations may have a non-specific deleterious effect—for example, by speeding up the process of ageing in the irradiated tissues—and they may have caused an occasional death from specific lesions such as radiation myelitis (Boden, 1950; Asscher and Anson, 1962).

Fifthly, other treatments may be harmful. Most patients received several forms of treatment and some deaths may have been related to the use of drugs—peptic ulcer, for example, possibly being due to the use of aspirin, phenylbutazone (Butazolidin), or cortisone.

Sixthly, some of the excess mortality may be an artifact due to the selection of imperfectly comparable death rates for the calculation of the expected mortality. The spondylitic patients may have included a lower proportion of men and women in the Registrar-General's upper social classes than the country as a whole, and the omission of Scottish experience from the national rates will have resulted in a slight underestimate of the expected mortality from some diseases.

Whether radiation produced any non-specific "ageing" effect cannot be determined from these data alone. Certainly the other explanations offered could account for much of the increased mortality; but whether they could account for it all cannot be decided in the absence of detailed information about patients treated by other methods. We are studying a group of spondylitic patients who have not been given radiotherapy, but it has proved difficult to collect a large group who have been followed for a long time, and it will be several years before any substantial results are observed. Meanwhile the constant ratio at all periods after the date of entry into the series between (1) the actual number of deaths from all diseases other than those in class C, and (2) the expected number calculated from national mortality rates, suggests to us that this excess mortality is likely to be dependent on the disease process and unrelated to the form of treatment.

Leukaemia

In contrast to the above, the excess deaths due to conditions in class C bear a clear relationship to the date of irradiation. Much other evidence has implicated ionizing radiations as a cause of leukaemia (see United Nations, 1964), and the new evidence obtained from these observations will not be discussed in detail here. We would add only that: (1) the 60 deaths attributed to leukaemia by the end of 1962 include only one death attributed to chronic lymphatic leukaemia, and in that case the clinical and cytological description proved to be mistaken[7]; (2) review of the evidence confirmed the diagnosis of leukaemia in all cases but one; and (3) some of the cases may be attributable to repeat courses of radiation given some years after the initial course which brought the patient under observation.

The possibility that a drug, or the disease itself, may play some part in the production of leukaemia has to be considered; but, in the light of all the other evidence and the time-relations observed in the present study, we see no reason to doubt that the excess deaths due to leukaemia (less three in which leukaemia was present when radiotherapy was started[8]) were due to the treatment—that is, 44 deaths by the end of 1959 and 49 by the end of 1962.[9] To these should be added some of the excess deaths attributed to aplastic anaemia, many of which were unrecognized cases of aleukaemic leukaemia—particularly those occurring more than three years after the start of treatment. In all, the total leukaemia mortality attributable to radiotherapy has been of the order of 60 per 15,000 persons, or 4 per 1,000 over a follow-up period averaging 13 years from the date of first observation. This estimate will presumably be increased with more prolonged observations, but the incidence of new cases appears to be falling off after 15 years, and it may not be increased much above the present figure.

Other Types of Cancer

Less evidence is available in relation to other types of cancer. Several individual types are known to be capable of induction

[7] Court Brown and Doll (1957), Case 1.
[8] Court Brown and Doll (1957), Cases 15, 33, and 34.
[9] The one death in which the presence of leukaemia was not confirmed has been subtracted.

by large amounts of radiation—in particular carcinoma of the pharynx, bronchi, and skin, sarcoma of the bones and soft tissues, and endothelioma of the liver. Exposure to moderate amounts of radiation in childhood has produced cancer of the thyroid, and it seems probable that exposure to small amounts of the order of 1–10 rads *in utero* produces all the principal types of childhood cancer. Mortality rates from all cancers other than leukaemia were raised in American radiologists compared with those in specialist physicians and ophthalmologists and otorhinolaryngologists (Seltser and Sartwell, 1965), and both the mortality and the morbidity rates from cancer other than leukaemia are slightly raised among the heavily exposed survivors of the Hiroshima and Nagasaki explosions compared with the rates among the distant survivors who were effectively not exposed to ionizing radiations at all (Jablon, Ishida, and Yamasaki, 1963 ; Harada, Ide, Ishida, and Troup, 1963). A clear increase in the prevalence of lymphomas other than leukaemia among the heavily exposed survivors has also been demonstrated (Anderson and Ishida, 1964).

In the present study two observations suggest that the increased mortality rate from cancer is largely an effect of radiotherapy. First, the increase is greater for cancer of sites that have certainly been fairly heavily irradiated than for cancer of other sites, many of which must have received little or no irradiation from the standard course of treatment. Secondly, the time relations between the appearance of the increase and the date of treatment are those that would be expected on clinical grounds if the two were causally related—that is, excess deaths began to appear about six to eight years after treatment and subsequently increased in incidence with the passage of time until 15 years after treatment or longer. The fact that the increase is widely spread among different types of cancer is also an indication that it is due to a non-specific carcinogenic factor. An increase in bronchial carcinoma alone, for example, might have been due to a tendency for spondylitic patients to smoke more (if such a tendency were shown to exist). There is, however, no known factor other than radiotherapy which could account for an increase in so many different types. The possibility that ankylosing spondylitis may create an increased susceptibility to cancer induction must be considered, but it seems unlikely in view of the two specific observations that have been referred to previously. It remains a possibility, however, until a sufficient series of observations have been made on patients treated by other methods.

On present evidence we conclude that the increased mortality from cancers of heavily irradiated sites (other than cancer of the colon) that appeared more than five years after irradiation is due to the treatment. We estimate, therefore, that the excess mortality, attributable to irradiation is of the order of 90 per 15,000 patients or 6 per 1,000 over a follow-up period averaging 13 years from the date of first observation. Contrary to the position with regard to leukaemia, however, there is no evidence to suggest that the main impact of the effect is yet passed, and the mortality attributable to radiations may increase two-fold or more with the further passage of time.

Summary

A total of 14,554 patients with ankylosing spondylitis, who were treated with *x* rays during the period 1935–54, have been studied. More than 98% were traced on or after 1 January 1960, and less complete follow-up information is available for a further three years.

The effects of irradiation have been assessed by comparing the numbers of deaths observed with the numbers that would have been expected if the patients had suffered the death rates recorded in the population of England and Wales as a whole. The most important finding, apart from the previously reported excess of deaths from leukaemia and aplastic anaemia, relates to other cancers originating in heavily irradiated tissues. Deaths attributed to these cancers were increased approximately twofold six or more years after first treatment, and 15 years after first treatment the excess showed no sign of diminishing. The excess was not limited to one or two types of cancer, but many different types contributed to it, approximately in proportion to their normal incidence. In contrast to these findings the number of deaths from cancers originating in lightly irradiated tissues was not increased significantly.

It is estimated that in an average follow-up period of 13 years after first treatment the excess deaths from leukaemia and from other cancers arising in heavily irradiated tissues, which can be attributed to the effects of ionizing radiations, were 4 per 1,000 patients and 6 per 1,000 patients respectively.

Deaths ascribed to spondylitis or rheumatism or to the direct complications of spondylitis were increased, as were to a less extent deaths due to a variety of other causes. Many different factors probably contributed to this, but their importance cannot be finally evaluated until results are obtained from a similar study of spondylitic patients treated by other means.

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